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Aviation, Space and Environmental Medicine *Review Article*

Hypercortisolism as a potential concern for submariners

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ABSTRACT

Cortisol is a stress-response hormone that is important for survivability in fight or flight situations. Hypercortisolism is a state of chronically elevated cortisol levels due to a failure to return to, or maintain baseline levels. It is a condition that is often undiagnosed and can aid in the development of many physiological and psychological health problems. Some of the health ailments associated with hypercortisolism include metabolic syndrome, decreases in bone mineral density, and depression. Chronic stress and sleep deprivation are two common causes of hypercortisolism; both areas of concern within the submarine community. This review discusses the etiology of hypercortisolism and the likelihood of submariner vulnerability to the condition along with health problems associated with it. Lastly, strategies to prevent chronic elevation of cortisol and mitigate the potential health risks associated with the condition are covered.

Important words: *Cortisol; Metabolic Syndrome; Exercise; Depression; Fatigue; Sleep*

What is Hypercortisolism?

Cortisol is a stress-response hormone, released from the adrenal cortex, which binds either mineralocorticoid receptors (MR) or glucocorticoid receptors (GR). Release of cortisol by the adrenal gland is controlled by pituitary secretion of adrenocorticotropin (ACTH), which is controlled by the hypothalamic secretion of corticotropin releasing hormone (CRH). Together, this is known as the hypothalamo-pituitary-adrenocortical axis (HPA axis). When cortisol levels increase beyond the baseline set-point, the pituitary gland and hypothalamus sense the high cortisol levels and release of ACTH and CRH are inhibited (Figure 1).

[Figure 1 here]

The term "stress" is difficult to define, but may be referred to as an interpreted or real threat to the psychological or physiological integrity of an individual that results in behavioral and/or physiological responses (25). Biomedically speaking, the term stress often describes a situation in which catecholamines and glucocorticoids from the adrenal gland are elevated in response to an experience (25). The HPA stress-response mechanism is intended to be an acute response to improve survivability and protect the organism, with reestablishment of equilibrium in an expedient manner once the threat has diminished. During an acute stress-response in humans, cortisol is up-regulated and utilized to mobilize energy for the "fight or flight" response. When an organism suffers from long-term activation or a prolongation of the allostatic load (defined as the cost of chronic exposure to a fluctuating or heightened neural and neuroendocrine response resulting from repeated or chronic environmental challenge that an individual reacts to as being particularly stressful) (50), the system can become dysregulated and lead to a chronic disease state (48). Over-activation of the HPA system resulting in chronically elevated cortisol levels (hypercortisolism) commonly occurs during psychological stress when no "fight or flight"

response is needed (93), but since there is no clear beginning or end to this stress, the response it is often protracted (4). When elevated cortisol levels are sustained within the body adverse physiological and psychological states such as glucose intolerance, dyslipidemia, obesity, hypertension (all components of metabolic syndrome) (99), decreases in bone density (62), depression (9), altered mood state (95), and a decline in high-risk decision making (84) are observed.

Chronically elevated cortisol levels are detrimental to the health of an individual at all ages. Elevated cortisol levels have been associated with metabolic syndrome and individual characteristics of metabolic syndrome in both children and adolescents (81). Even over-exposure to cortisol in utero has been shown to impact the health and development of fetuses in both animals and humans, with potential increased risks for cardiovascular and psychological health problems later in life such as hypertension, type 2 diabetes, and posttraumatic stress disorder (PTSD) (69, 80). Clearly, proper regulation of the HPA stress-response axis is vitally important to the maintenance of physiological and psychological health of the individual.

Cortisol levels have been shown to increase acutely in multiple stressful military situations (87, 92), however it is not known if submariners are vulnerable to chronic increases in cortisol levels in response to challenging work demands and fatigue. With the constant work and sleep challenges that sailors often face in a submarine deployment, it is possible that submariners are vulnerable to hypercortisolism and all of the physiological and psychological consequences associated with it. To date, various reviews have been written warning of the negative effects hypercortisolism has on physical (1, 62, 96) and psychological health (9), along with ways to mitigate these negative consequences (93), but none have been written pertaining to the sustainment of submariner health and performance. Commonly, the term hypercortisolism is

used interchangeably with the term Cushing's syndrome or "overt hypercortisolism", which can be used to mean chronically elevated cortisol levels as a result of various causes including glucocorticoid administration for suppression of inflammatory or immune response, or adrenal and pituitary tumors. In order to avoid confusion over the term hypercortisolism, from this point on the term hypercortisolism will be used in reference to a chronic excess of cortisol as a result of chronic stress or sleep deprivation and fatigue. This type of hypercortisolism often goes undiagnosed due to a lack of clinical symptoms and is sometimes referred to as "subclinical hypercortisolism".

Causes of Hypercortisolism?

In humans, the normal circadian rhythm of cortisol includes a rise and peak of concentrations in the waking hours (acrophase), followed by declining levels throughout the rest of the morning until a small spike occurs in the early afternoon. Levels then continue to decline, except for a mini-spike in the evening, until finally a quiescent period with minimal secretion during nighttime resting hours (lowest cortisol levels of the cycle) is achieved (2). This daily rhythm of cortisol is depicted in Figure 2 (47). Chronic stress is often instrumental in the induction of hypercortisolism (4). During the state of chronic stress, a decrease in the diurnal variability of cortisol levels is observed (39). This causes a cortisol plateau effect, negating the sharp increases and decreases seen in a normal daily rhythm (Figure 2), resulting in chronically elevated cortsiol levels. Some stressors implicated in inducing hypercortisolism include chronic work stress (24), anxiety (13), and low socioeconomic status or unemployment (46).

[Figure 2 here]

Sandal *et al.* (74) suggest that individuals exposed to working in extreme and isolated environments encounter physical and psychosocial stressors beyond those that occur in the

normal workplace. They also note decreases in work performance and emotional lability, along with increased occurrence of depressive mood, psychosomatic complaints, interpersonal conflict, and lapses of attention (74). This is interesting because submariners work in a setting where they are often isolated physically (e.g. no exposure to sunlight, fresh air, room to move freely) and psychosocially (e.g. friends, family, television, and news) from the world for an extended period of time (sometimes 3 months or more). Furthermore, submariners face other unique work and living conditions that can be physically and psychologically challenging such as paucity of personal and physical space, limited exercise facilities (~5 exercise machines total per boat), a tiny rest area (rack) that is sometimes shared by two submariners at alternating times (hotbunking), constant dim lighting, 18-hour watchstanding cycles, and an overabundance of food consumption opportunities (4 meals served per 24 hours). Unsurprisingly, a study involving submariners from the Royal Navy (RN) found that submariners report significantly higher levels of stress (40%) compared to shore-based (25%), overseas (30%), and overall personnel (28%) (6). Self-report stress levels in the US Navy have not been analyzed yet, but considering the great work demands present among the crew of US submarines, it is reasonable to assume these stress rates are similar among US submariners. Admittedly, it may be true in some cases that submariners face adverse health effects from stress without hypercortisolism being the cause, however, chronic cortisol levels as a physiologic measure of stress have not been quantified in submariners at sea and compared to those serving at shore commands in either the RN or the US Navy. It is very possible that submariners are more vulnerable to hypercortisolism while underway due to heightened stress levels.

Sleep deprivation is another factor that has been implicated in the induction of hypercortisolism (2). Spiegel *et al.* (83) observed an increase in evening cortisol levels in young

men restricted to 4 hours of sleep per night for 6 days. Additionally, rises in cortisol were also reported after one night of full sleep deprivation in military (28) and non-military settings (79). Moreover, another study looked at cortisol levels 2 days prior to duty (a period of work), 7 days during duty, and 2 days following duty of German emergency helicopter pilots who had long duty hours (sometimes up to 15.5 hours) and reduced sleep time (total of ~15 h of sleep debt per duty period). The mean cortisol levels of the pilots were significantly increased (50-80%) during duty as well as for the 2 days following duty (73). This suggests chronic fatigue and sleep debt has long lasting effects on cortisol levels, even if one makes an attempt to catch up on lost sleep.

Sleep deprivation and fatigue are major concerns among the submarine force. In a study done aboard a US submarine, Kelly *et al.* observed an average of 7 hours of sleep among submariners over a 24 hour period, but also noted that sleep episodes only averaged 5.5 hours in duration, indicating sleep is often broken up into segments over a 24 hour period (36). Similarly, a more recent study examining the 18-hour watch schedules performed among US submarines found that submariners average a total of 7.1 hours of sleep over a 24 hour period. Although the average length of sleep per sleep episode was not reported, the authors reported that cognitive performance tests indicated a level of performance of only slightly better than what is expected from 24 hours of continued wakefulness (or a blood alcohol level of 0.10%) as estimated by the Department of Defense Sleep, Activity, Fatigue, and Task Effectiveness (SAFTE) simulation program, the Fatigue Avoidance Scheduling Tool (FAST^{TM}) (23), suggesting the submariners in this study may have been fatigued. Many other factors could also be contributing to the lower than expected scores, however fatigue may be the major component as other investigators have noted that the 18 hour “day” of a US submariner leads to a circadian disruption similar to the daily experience of traveling eastward across 6 time zones (e.g. New York City, USA to Rome,

Italy), resulting in sleep deficit and a chronic jet-lag effect (51). Curiously, neither of these reports commented on sleep efficiency, defined as total sleep time divided by total time in bed, in submariners while underway, which is another important factor that may impact chronic cortisol levels and overall health. The results of one study not conducted on a submarine, however, found that circadian misalignment can cause decreased sleep efficiency (-17%) along with other physiological changes such as decreased leptin (-17%), increased glucose (+6%), increased insulin (+22%), increased mean arterial pressure (+3%), and a reversal in daily cortisol rhythm (76). The consequences of circadian misalignment and reduced sleep efficiency found in this study are of interest because in addition to the continuous circadian disruptions submariners face, sleep efficiency may also be reduced as has been noted during general military deployments. For instance, it was observed that while deployed 40% of military members have a sleep efficiency of <85% (85% is normal) while 42% have a sleep onset latency of >30 minutes (15 minutes is normal), and both measures were significantly worse in night shift workers compared to day shift. Also, 74% of participants in this study rated their quality of sleep as significantly worse in the deployed environment (63). Ultimately, while sleep efficiency among submariners has not been reported, these studies taken together suggest that the lifestyle of the submariner could very well make individuals more vulnerable to the consequences seen in the circadian misalignment study by Scheer *et al*. (76) as the dynamics of the study are very similar to the experience of the US submariner.

Hypercortisolism and Metabolic Syndrome

Metabolic syndrome is one of the most serious health disorders facing the world in the modern era as one quarter of the world's adult population is thought to suffer from it (88). Individuals with metabolic syndrome have doubled odds of cardiovascular mortality and are

three times as likely to suffer from a heart attack or stroke (42). The National Cholesterol Education Program (NCEP) Adult Treatment Panel-III (ATP-III define metabolic syndrome as having three or more of the following : fasting glucose of at least 110mg/dl, blood pressure of at least 130/85, waist circumference of greater than 102 cm in men and 88 cm in women, triglycerides greater than150 mg/dl, and HDL cholesterol (commonly referred to as "good cholesterol") of less than 40 mg/dl in men and 50 mg/dl in women (89). An interesting observation was previously made potentially linking excess cortisol levels to metabolic syndrome; namely those with metabolic syndrome share similar characteristics to those suffering from Cushing's syndrome. This observation led to the idea that hypercortisolism may play a significant role in the pathology of metabolic syndrome (1, 96). Indeed, as expected, researchers started to find that patients with metabolic syndrome have higher urinary free cortisol excretion values (22, 52, 81). Additionally, elevated cortisol levels were found to be associated with individual characteristics of metabolic syndrome. For instance, hypertension has been shown in multiple studies to be associated with increased cortisol levels (22, 52, 65). This is possibly attributed to stress (27), or could also be due to an increase in vascular responsiveness to vasoconstricting agents and decreased availability of the vasodilating agent nitric oxide (53). Also, elevated cortisol levels are associated with high triglyceride and low HDL cholesterol levels (22, 65, 96), along with increased fasting glucose concentrations (22, 65, 97). Furthermore, evidence has been found implicating cortisol in the development of non-diagnostic features of metabolic syndrome. Both endothelial dysfunction and elevated serum uric acid levels, which raise the risk for cardiovascular disease, coronary heart disease, and stroke, are common features of metabolic syndrome and are also observed in patients with Cushing's syndrome (3, 38, 94).

Interestingly, observations have been made in animals and humans implicating chronic psychological stress in the development metabolic disorders. In a murine study, chronic stress was shown to induce hyperglycemia, dyslipidemia, increased amino acid turnover, acidosis, loss of lean body mass, alterations in expression of metabolic genes, hypercortisolism, hyperleptinemia, insulin resistance, and hypothyroidism (18). Although these data provide strong evidence for an association between chronic stress and metabolic syndrome, it is worth mentioning that the changes in expression of metabolic genes were reported to be much less pronounced after an acute stress exposure, suggesting chronic stress is a prerequisite for the manifestation of adverse metabolic changes. Shively *et al.* made similar observations in non-human primates. In this study, where subordinate monkeys were exposed to constant aggression from dominant monkeys within a social group, the physical and psychological stress leads to hyperglycemia and insulin resistance, elevated blood pressure, coronary artery atherosclerosis, increased visceral fat deposition, elevated total cholesterol with decreased HDL cholesterol, hypogonadism, adrenal hypertrophy, and increased adrenal responsiveness to ACTH infusions (82). Conclusions from the human study named the Whitehall II study concur with the animal findings. This study was conducted over a 14-year period examining over 10,000 civil servants and found a dose-response association between work stress and metabolic syndrome and concluded that individuals exposed to chronic work stress are more than twice as likely to develop metabolic syndrome than those without stress at work (8).

It appears glucocorticoid (cortisol in humans, corticosterone in rodents) levels may also be instrumental in determining how much and which types of food will be preferred for consumption. According to studies conducted in rats, stress and resultant glucocorticoid levels have been observed to stimulate the desire to increase the intake of lard and sucrose (comfort

foods) (14-16). Additionally in rats, glucocorticoids have been shown to antagonize leptin (a hormone in the body released by fat cells to reduce food consumption) sensitivity, resulting in obesity (101). In humans, increased cortisol levels from stress seem to coincide with increased levels of neuropeptide Y (stimulates appetite) consequently leading to a potential increase in food-seeking behavior (54, 55). Furthermore in humans, while evidence varies depending on the type of stressor, greater preference for foods high in sugar and fat seems to be associated with chronic life stress, as is observed in the rat studies mentioned above (90). Moreover, longitudinal studies suggest that chronic life stress may be causally linked to weight gain, especially in men (90). The jury is still out on exactly how much cortisol influences food consumption in humans, but this evidence suggests excess cortisol may influence individuals in their decision of what and how much to eat, which in turn may further contribute to the metabolic and cardiovascular disorders already associated with hypercortisolism.

In the current submarine community, physical fitness and cardiovascular health are a major concern. An interesting study performed at NSMRL examined the occurrence of metabolic syndrome within the submarine population at SUBASE New London through screening submariner medical records. Although the sample size was low (n=199), it was observed that 19.1% of submariners between the ages of 30-44 have metabolic syndrome according to the ATP-III standards (30). In terms of matching the typical age with the ranks that are most commonly represented within the 30-44 age-range, these data indicate that approximately 1 out of every 5 first class petty officers and above (E6-E9) among the enlisted ranks, and 1 out of every 5 lieutenants and above (O3-O6) among the officer ranks, have metabolic syndrome on submarines. This leaves a striking percentage of the leadership among boats with a significantly increased risk for heart attack or stroke. At this point it should be

considered, however, that metabolic syndrome is a condition that takes time to develop. Although energy intake and expenditure, physical activity, and chronic stress levels have not been determined in submariners, one would think that the submarine lifestyle at all ages is not conducive to the prevention of metabolic syndrome and maintenance of cardiovascular health, and cortisol may be playing a key role in the development of these malefactors.

Effects of Hypercortisolism on Bone Density

Maintenance of appropriate vitamin D and calcium levels are the best ways to preserve bone health. Hypercortisolism can negatively affect bone density and may be another serious piece of the puzzle when it comes to attenuating bone loss. This idea is highlighted by the finding that bone turnover is suppressed in the presence of elevated cortisol, which may lead to osteoporosis in vulnerable individuals (10, 12). In fact, osteoporosis and vertebral fracture is observed in up to 70% of patients suffering from Cushing's syndrome (overt hypercortisolism), a well-known secondary cause of osteoporosis (12). Additionally, multiple studies suggest individuals with subclinical hypercortisolism are also at risk for osteoporosis and vertebral fractures (11, 20, 70), although prevalences appear to be lower in subclinical hypercortisolism cases than in overt hypercortisolism (10.8% vertebral fracture and 4.8% osteoporosis) (10). These percentages are difficult to determine, however, due to a common lack of diagnosis of subclinical hypercortisolism.

Mechanistically speaking, excess cortisol has been shown to inhibit osteoblastogenesis (100), while inducing apoptosis of osteoblasts and osteocytes (60), resulting in less osteoblastic cells (opposite of vitamin D actions). This is not the only way cortisol affects bone health, however, as hypercortisolism may also disrupt calcium homeostasis. Whereas vitamin D acts to increase intestinal absorption and renal tubule re-absorption of calcium, these actions have been

observed to be decreased in patients with elevated cortisol levels (56, 68), thus leaving less calcium for new bone formation.

Bone health is another health concern for submariners and has been the subject of multiple studies aboard US submarines. One study found that over a 68 day patrol, 25-(OH) vitamin D levels dropped significantly, whereas parathyroid hormone (PTH) levels increased (21). Additionally, Schlichting *et al*. (77) also reported a decrease in 25-(OH) vitamin D levels over a 2 month deployment. Moreover, a recent study of Israeli submariners found that a 30 day submersion led to decreased bone density and 25-(OH) levels, but it also led to decreased circulating PTH levels and bone remodeling markers, along with increased circulating calcium levels (44). Taken together, these data suggest that deployments of ~2 months result in bone resorption, but deployments of 1 month may only result in reduced bone metabolism. However, it is not known whether bone mineral density is decreased over the course of a submariner's career. Since recent evidence suggests cortisol has opposite actions on bone generation than vitamin D, it is reasonable to speculate that submariner bone density may be negatively impacted from both excess cortisol and decreased 25-(OH) vitamin D levels. More research is needed before final conclusions can be made about the impact of submarine life on bone density and health.

Hypercortisolism and Psychological/Cognitive Issues

In addition to physiological consequences, hypercortisolism also negatively impacts psychological health and cognitive ability. In nearly 50% of depression cases, increased cortisol secretion is observed over a 24 hour period (29, 64, 71). In a study consisting of 15 severely depressed male patients not on psychotropic drugs and 22 age-matched controls, Deuschle *et al.* (19) observed that mean 24 hour cortisol and ACTH were significantly higher in depressed

patients. Concurrently, they found that frequency of cortisol and ACTH pulses were increased and there was a reduced time of quiescence in the depressed patients (19). Intriguingly, another study examined the brains of 6 depressed suicides and found there to be a 4-fold increase in the number of cells expressing CRH in the paraventricular nucleus, suggesting an increase in central drive due to depression or intense stress hours prior to suicide (66). Moreover, it has also long been known that depression is often seen in patients with Cushing's syndrome (37), and that metyrapone (inhibits cortisol synthesis) can successfully relieve depressive symptoms in Cushing's syndrome patients (35), suggesting the excess cortisol may be causal of the depression, at least in this population. Depression rates within the Navy and Submarine community are not known, but according to an entry level Army sample more than 15% of men (general population male depression rate is 7-12%) and 22% of females (general population female depression rate is 20-25%) showed signs of moderate/severe depression (98), indicating prevalence of depression may be higher in military men than in the general population.

Evidence also suggests that prolonged exposure to elevated cortisol levels can affect the structure and function of the hippocampus, adversely affecting cognition and memory (75). This is observed in individuals suffering from PTSD as they have been shown to have experienced hippocampal atrophy (49). Multiple sources of evidence indicate the hippocampus is also a regulator of the stress response axis (HPA) in addition to its role in memory and cognition (32-34). Ultimately this leads to the idea that chronically elevated cortisol levels may physically alter the neural structures involved in negatively regulating the stress response, causing a more persistent stress reaction. Interestingly, anticipatory stress leading to increased cortisol levels has been shown to adversely affect decision making when risk is involved, even when information about outcome contingencies is available (84). This is noteworthy because many operational

decisions made while underway can involve risk. It is not known to what degree hypercortisolism affects the psychology, morale, and cognitive ability of sailors among submarines, but it is surely in the interest of the crew to take the necessary steps to reduce the potential for crewmembers to become hypercortisolemic.

Ways to Mitigate the Potential for Hypercortisolism and its Health Risks

Regular exercise is an important and relatively easy way that a sailor can promote physiological and psychological well-being. Many studies indicate that exercise makes an individual more resistant to stress (31, 78, 86) . Specifically, it has been observed that superior physical fitness reduces the response to psychological stressors, and also provides psychological and cognitive benefits including improvements in mood, cognitive ability, and depression and anxiety scores (7). Additionally, in a study of over 32,000 people, it was discovered that less active people reported high stress levels twice as much as those who were more active (85). Similarly, a population study in Finland concluded that there is an association between exercise and psychological well-being (31). Moreover, in another study of over 12,000 men and women it was observed that those who are sedentary are more prone to stress and life dissatisfaction than those who are active in their free time (78). Interestingly, within the military it has been observed that physical fitness may reduce stress symptoms during extreme training (86), suggesting physically fit military members may perform better in intense or stressful situations than unfit individuals due to a reduced stress response. Furthermore, complex decision making has been observed to improve amidst sustained stress with moderate exercise (43). The mechanism by which individuals who exercise become less vulnerable to stress is unclear, but one thought is that exercise training may help reduce the HPA axis sympathetic nervous system (SNS) response to stressful stimuli. Evidence for this hypothesis has been found in studies

where individuals who exercised regularly and were fit had low catecholamine and cortisol levels and reduced SNS and cardiovascular response when confronted with stressful stimuli (5, 91).

In addition to stress reduction, exercise can help prevent the hippocampal neuronal degeneration often seen with chronic overexposure of the hippocampus to cortisol. Brain-derived neurotropic factor (BDNF), which helps regulate neuronal differentiation and synaptic plasticity in rodents (41), is decreased in the hippocampus in response to chronic stress (59). Exercise, however, has been shown to increase BDNF levels in the hippocampus and protect against neuronal degeneration (58).

Multiple studies suggest symptoms of depression can be lessened by regular exercise. One report shows that exercise, when compared with no treatment, reduces symptoms associated with depression according to the Beck Depression Inventory (40). Another study discovered that exercise reduces the amount of urine cortisol and reduces the depressive state in adolescent females (57). One reason exercise may aid in mitigating symptoms of depression is that it promotes serotonin and dopamine secretion (67). Another possibility is that exercise may increase endogenous opioid activity in the central and peripheral nervous system which could help fight depression (and stress) (72).

In addition to the benefits already discussed, cardiometabolic disorders associated with chronically elevated cortisol are also drastically improved with regular exercise. Central obesity, insulin resistance, glucose intolerance, dyslipidemia, and stress-mediated hypertension are positively affected by regular exercise (93). The obvious benefits that regular exercise has on preventing stress and elevated cortisol levels, overall mental health and cognition, and cardiometabolic health make it imperative that submariners strive to exercise regularly. An

optimal recommendation would be to follow the American Heart Association's (AHA) guide for exercise and fitness and get at minimum 30 minutes of moderate exercise 5 days a week (26).

Several other factors have been shown to help prevent chronic elevation of cortisol levels within the body. As mentioned previously, sleep deprivation can lead to chronically elevated cortisol levels. It is important therefore for submariners to not only be aware of the role fatigue has in hindering performance and increasing risk for operational mishaps, but also be aware of detrimental effects it has on their overall health. One way to potentially aid in fatigue prevention would be to reconfigure watch schedules to allow for 24 hour daily cycles, such as 8 hours on watch and 16 hours off, as this may be conducive to obtaining longer uninterrupted rest periods for submariners. Under current conditions, however, submariners should strive for the maximum amounts of uninterrupted sleep possible within the18-hour "day" they operate under in order to reduce the harmful consequences of fatigue. Meditation (45) and religiosity (17) have also been shown to mitigate the effects of chronic stress by lowering chronic cortisol levels, suggesting various mental relaxation techniques may be beneficial to submariners when not performing duties. Additionally, the U.S. Navy provides training sessions, both at training schools and while underway on a submarine, for various situations the submariners are put into with the hopes that submariners will react with better performance and less stress when these situations arise during an operational situation. While this may help eliminate some operational stress, it still may not substantially contribute to a reduction in the overall stress levels felt from a constantly high workload with little sleep on top of the unique working conditions that submariners face. Stress resiliency training is another potential tool for reducing stress in submariners, however this is not currently provided in the U.S. Navy. Lastly, there is preliminary evidence that cortisol levels may be able to be controlled pharmaceutically. Metyrapone, which is a drug that blocks

synthesis of cortisol in the adrenal gland, has been used in studies with marginal success. For example, one placebo controlled study reports metyrapone possesses an antidepressant effect through inhibiting cortisol (61). The problem with this strategy, however, is that it may leave an individual at risk for an inadequate HPA response during a stressful "fight or flight" situation, and is therefore not optimal for long-term therapy at this time. This presently leaves the conglomeration of exercise, sufficient rest, and mental relaxation techniques as the best combined strategy to fight hypercortisolism.

Conclusions

Hypercortisolism is a state of over-activation of the HPA axis in which the negative feedback elements are not properly regulating the system (Figure 1), ultimately resulting in chronically elevated cortisol levels. Cortisol spikes are needed in fight or flight situations, but constant activation can lead certain illnesses and disease states. Chronic stress, sleep deprivation and fatigue are primary causes of hypercortisolism, and by the nature of their work submariners may be more vulnerable to developing this condition. This may be worrisome because hypercortisolism has been linked to various adverse conditions such as metabolic syndrome (and individual components of), decreased bone density, and depression (Figure 3). Certain measures, however, can be taken to help reduce the vulnerability to hypercortisolism including regular exercise, efficient rest periods that are sufficient in length, and mental relaxation techniques such as those observed in religion and meditation (Figure 3). If, indeed, submariners are vulnerable to hypercortisolism, taking steps to minimize this condition may increase the long-term health and productivity of the submarine community.

[Figure 3 here]

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Figure Captions

1. Diagram of the different components of the HPA axis and how it interacts. CRH = Corticotrophin Releasing Hormone, ACTH = Adrenocorticotropin.
2. Diagram exhibiting the normal daily cortisol rhythm in humans (bolded line), adapted from reference 47, and the decreased diurnal cortisol variability resulting from chronic stress (dashed line); mcrg=micrograms, dL=deciliter.
3. Diagram of the multiple factors influencing chronic cortisol levels within the body and the health consequences that are associated with elevated cortisol levels. BP=Blood Pressure, FG = Fasting Glucose, HDL = High Density Lipids, CE = Comfort Eating, BD = Bone Density, and DM = Decision Making.

Figure 1.

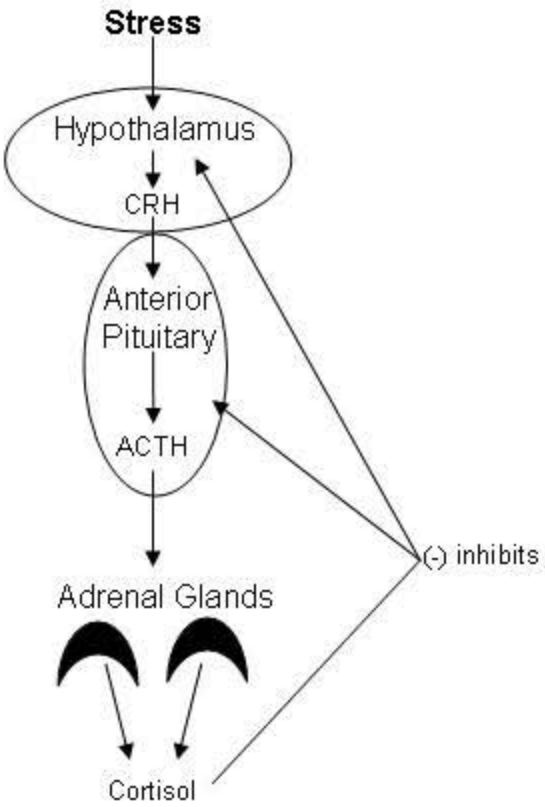

Stress
Hypothalamus
CRH
Anterior Pituitary
ACTH
Adrenal Glands
Cortisol
(-) inhibits

Figure 2.

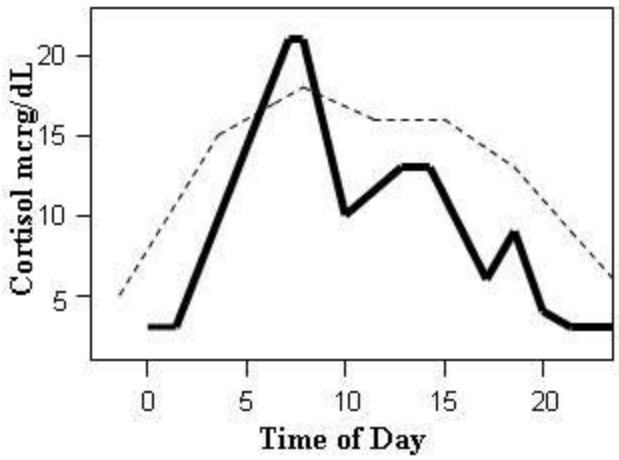
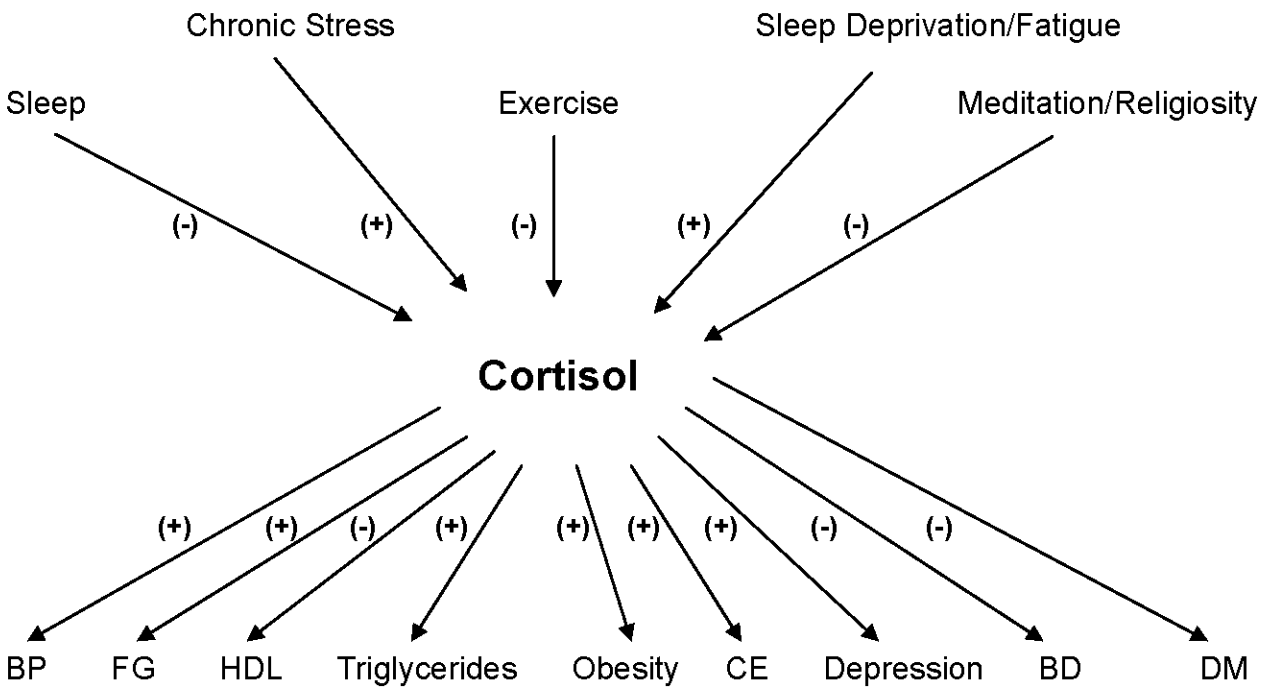


Figure 3.


Chronic Stress
Sleep Deprivation/Fatigue
Sleep
Exercise
Meditation/Religiosity
(-)
(+)
(-)
(+)
(-)
Cortisol
(+)
(+)
(-)
(+)
(+)
(+)
(+)
(-)
(-)
BP
FG
HDL
Triglycerides
Obesity
CE
Depression
BD
DM